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Inhalation Toxicology: XI. The Effect of Elevated Temperature on Carbon Monoxide Toxicity

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NOTICE

The animals used for this experiment were lawfully acquired and treated in accordance with the "Guide for the Care and Use of Laboratory Animal Resources," National Research Council, DHEW Publication No. (NIH) 74-23.

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16. Abstract

Laboratory rats were exposed (a) to experimental concentrations of carbon monoxide in air at ambient temperature, (b) to elevated temperature atmospheres from 40° C to 60° C, and (c) to selected carbon monoxide (CO) concentrations at the elevated temperatures in (b). The incapacitating potency of each of the environments was evaluated by measurement of time-to-incapacitation (t_i) as a function of CO concentration and/or temperature; incapacitation was defined operationally as loss of ability to walk inside a motor-driven, rotating cage enclosed in an exposure chamber. Comparison of data from the combined (CO + elevated temperature) exposures and exposures to CO and elevated temperatures alone indicated that incapacitation occurred earlier when CO inhalation was combined with a whole-body, elevated temperature environment than was observed for the same exposure parameters applied individually. No evidence for a synergistic effect was noted. An empirical equation was derived that allows the calculation of a predicted t_i for combinations of CO and temperature within the ranges utilized in the experimental exposures.

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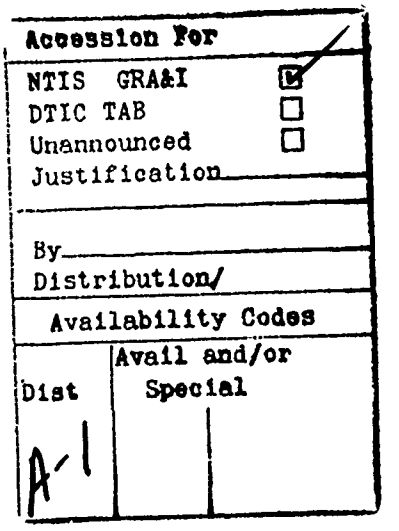

INHALATION TOXICOLOGY: XI. THE EFFECT OF ELEVATED TEMPERATURE ON CARBON MONOXIDE TOXICITY

INTRODUCTION

The use of the laboratory rat as an animal model for determining the toxicity of combustion gases is well established. Nearly all of the current assay methods in combustion toxicology utilize some physiological response of an experimental animal as a measure of the total toxicity of the inhaled gases. Although the rat conveniently integrates the effects of the multiple toxic gases produced from burning materials, other combustion-induced conditions of elevated temperatures and oxygen depletion can alter the degree of observed response unless these parameters are carefully controlled.

Previous work in this laboratory determined the time and temperature conditions required for heat incapacitation in rats and mice (1), and earlier work by Robinson (2) defined survival times in resting and exercising conditions at elevated temperatures. Although the commonly-observed animal responses (physical incapacitation, shock avoidance failure, and death) can be caused by hyperthermia alone, either from exposure to elevated ambient temperatures or from exhaustion-induced heatstroke, the more subtle effects of moderately elevated temperatures on the response to known concentrations of a single gas have not been quantitatively described. As part of our continuing program to study the effects of combinations of combustion products, this report explores the effects of whole body exposure to moderately elevated air temperatures (40 to 60° C) on carbon monoxide (CO) toxicity.

MATERIALS AND METHODS

Chamber Design: The exposure chamber used for this study was constructed by the authors from 1/2-inch polymethylmethacrylate (PMMA) sheets as shown in Figure 1; internal dimensions are 50.8-cm long by 26.6-cm wide by 50.6-cm high. The cylindrical rotating cage assembly (40.6-cm dia) has a plastic mesh floor (perimeter) and a perforated PMMA internal divider that acts as a central support. The cage was suspended across the width of the chamber by an axle passing through the central divider and connected to an external geared motor; the walls of the chamber functioned as exterior sidewalls for the cage. A gasketed door (10 by 10 cm) was installed in the side of the chamber at the level of the cage floor to allow rapid insertion and removal of

the test animals. The rotating cage was driven by a 4-rpm geared motor providing a circumferential velocity of 8.5 cm/s. Two plastic-bladed fans mounted on opposite ends of the chamber provided uniform thermal mixing and gas distribution.

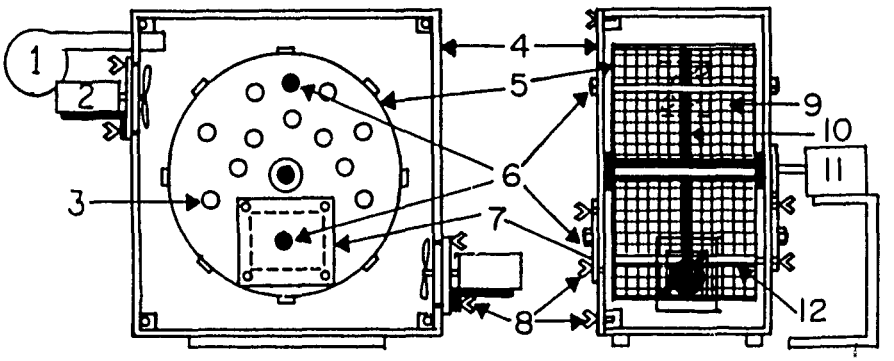

Figure 1. Animal Exposure Chamber

1. Modified heat gun (Master Appliance Corp., Racine, Wisconsin, model HG301).
2. Mixing fan assembly (1/15 hp motor, 5,000 rpm, fitted with 7-cm, 4-bladed Nylon fan).
3. Ventilation holes, 12-mm dia, cut through center divider of rotating cage.
4. Exposure chamber walls constructed from 1/2-inch (12-mm) thick polymethylmethacrylate.
5. Rotating cage assembly (divider and outer rim are 1/4-inch (6-mm) thick polymethylmethacrylate; surface is polyethylene mesh).
6. Gas sampling ports sealed with serum vial stoppers.
7. Chamber access port for animal insertion and removal.
8. Thumbscrew fasteners.
9. Polyethylene mesh cover, mesh openings are approximately 7-mm square.
10. Center divider and support for rotating cage.
11. Cage drive motor (4-rpm).
12. Cross supports for chamber rims and plastic mesh cover.

Animals: Male albino rats of Sprague-Dawley origin were obtained from Charles River Breeding Laboratories, Wilmington, MA, in a 100-200g weight range. They were inspected by a veterinarian upon arrival and held in isolation for 8 days prior to use. All rats were fasted overnight before testing to establish equivalent metabolic states.

Gas Handling Equipment: Carbon monoxide (research grade) and breathing air were mixed by passage through a baffled cylindrical mixing tube before entering the animal exposure chamber. The CO flow rate was regulated automatically by a Matheson model 8240 mass flow controller; air flow rates were controlled manually by use of a simple, tank-mounted, two-stage pressure regulator and needle valve assembly. Gas input into the chamber was through a port in the top near the heated air inlet; the exhaust port was located in the rear panel. The entire chamber was installed inside a fume hood into which the chamber exhaust was vented.

Temperature Control Equipment: To provide a regulated temperature in the 40-60°C range, we mounted a modified heat gun in the upper end of the chamber with the heated airflow in the direction of the cage rotation. Modifications included connecting the air intake to a return tube so that chamber atmosphere was recirculated through the heating coils in a closed cycle, and sealing the entire blower housing. The unit was rewired to allow constant blower operation with the heating coils controlled by thermistor input to a temperature controller, and with in-line heater voltage controlled by a variable transformer. This arrangement allowed the initial chamber temperature to be established quickly (at high voltage) and maintained with minimal fluctuation (at low voltage) due to the on/off application of power by the temperature controller.

Gas Analysis: The chamber atmosphere was analyzed for CO by gas chromatography, using a Carle series 100 gas chromatograph (GC) equipped with 1/8-inch packed columns and a thermistor detector. A continuous stream of chamber atmosphere was pumped from a sampling port about 2 cm above the head of the walking rat, routed through the GC sample loop, then back to the chamber. The flow rate of 55 mL/min was maintained by a ceramic piston pump (FMI model RRP, Fluid Metering, Inc., Oyster Bay, NY). Injections were accomplished automatically by activating the sample injector valve with an interval timer. The initial sample (after rat insertion) was injected at 1 min; additional samples were injected at 1.5-min intervals, the minimum allowed by the CO retention time. Concentrations were determined by comparison of peak height to a standard curve prepared by operating the injector valve while flowing syringe dilutions of tank CO and air through the sample loop at the same 55 mL/min rate used in the automatic sampling system. Initial tests indicated that a 4 L/min airflow was adequate to insure the maintenance of the ambient oxygen level with single rat exposures; therefore, chamber oxygen was not monitored during subsequent analyses.

Test Atmosphere Generation: With the chamber assembled and the vent open, compressed air flow was adjusted to 4 L/min with the in-line needle valve. The temperature controller was set at the required chamber temperature and the blower, mixing fans, and cage rotation motor were turned on. Carbon monoxide flow was set

on the mass flow controller at the levels calculated to produce the desired concentration when diluted by the 4 L/min airflow. Pure CO was manually injected into the chamber in a volume slightly less than that required to quickly adjust the concentration to the experimental level. When an equilibrium concentration was reached (as indicated by the 1.5-min interval monitoring), any minor concentration adjustments were made by adjusting the CO volume input with the mass flow controller.

Test Procedure: When gas concentration and/or chamber temperature reached the desired equilibrium conditions, a final pre-insertion sample was injected into the GC; the fans and cage motor were turned off. The sampling timer was reset to zero and the retaining screws on the chamber access door were removed in preparation for rat insertion. In rapid sequence, the door was opened, one rat was inserted, the door was closed, and the timer, fans, and cage motor were activated. A chromel-alumel thermocouple, suspended 2 inches above the nose of the walking rat, provided continuous recording of chamber temperatures; GC peak traces and the associated chamber temperatures were recorded synchronously using a multichannel strip recorder. Sampling was continued at 1.5-min intervals until the rat could no longer continue walking in the rotating cage and began to tumble or slide. Time-to-incapacitation (t_i) was then recorded and one additional gas sample was taken to provide a continuous concentration record from insertion through t_i. At this point, the fan, sampling timer, and cage motor were turned off. The rat was removed from the exposure chamber and placed in a small chamber containing a high concentration of CO, and was left until respiration ceased. The animal exposure system is depicted schematically in Figure 2.

Relative humidity (RH) inside the chamber was noted, but not controlled. The 4 L/min airflow provided an 8 to 10% RH at the beginning of each experiment; maximum RH was 28% (at t_i) for the 60°C studies and 58% for the 40°C studies for temperature effects alone (i.e., without CO). Humidity remained well above the <5% level at which dehydration normally occurs (3,4).

The temperature/response relationship was determined by exposing 32 rats, individually, to environmental temperatures of 40 to 60°C, in 5° increments, and measuring t_i with continuous temperature monitoring. The concentration/response for CO alone was determined in the same system by exposing 43 rats, individually, to mean CO concentrations over the range of 995 to 9111 ppm (v/v).

The effects of elevated temperature on CO response were measured by exposing rats to nominal CO concentration levels of 1000, 1600, and 3100 ppm (that normally result in 43, 23, and 11 min t_i's respectively at ambient temperature) combined with elevated chamber temperatures from 40 to 60°C (using 5° intervals), i.e.,

1000 ppm CO at 40°C, 1600 ppm CO at 40°C...3100 ppm CO at 60°C. Sixty-three rats were exposed to these combinations of CO concentrations and elevated temperatures; t_i was recorded for each exposure.

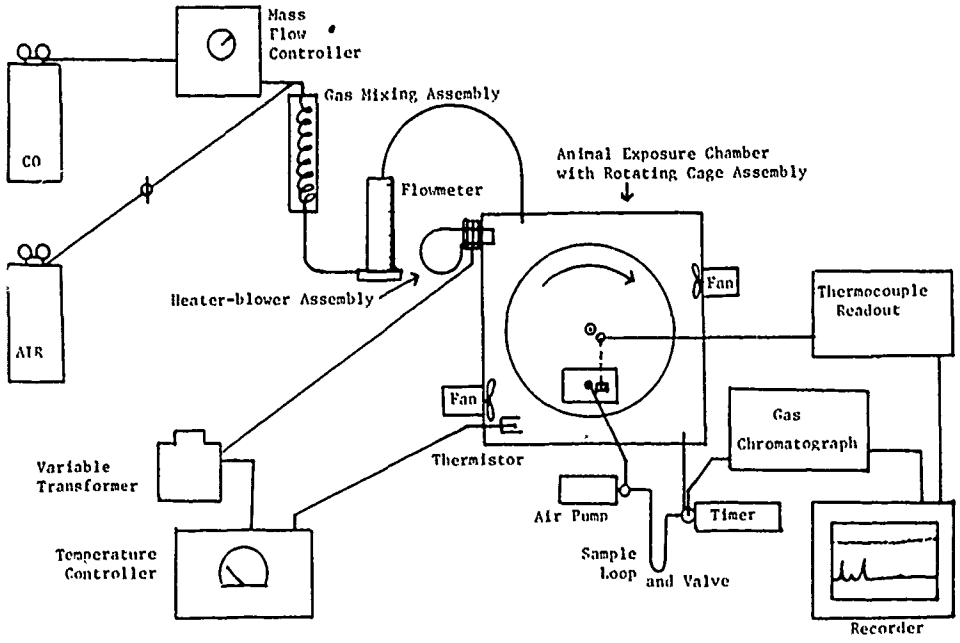

Figure 2. Animal Exposure System

RESULTS AND DISCUSSION

Continuous walking in the rotating cage limited the saliva spreading activity that is critical to body-temperature regulation in the rat (5), and the use of male rats may have indicated a higher degree of thermal resistance than would have been shown with female rat subjects. Actual physical activity was moderate; the walking speed of 8.5 cm/s (0.19 mph) was well below the 1 mph required by Gollnick and Ianuzzo (6) to reach a plateau core temperature of 40.2°C. The rectal temperatures, for rats exposed to elevated temperatures only, averaged 43.5°C (s.d.= 0.80) at incapacitation, which corresponded well with the 40.4 to 43.0°C temperature range recorded at exhaustion by Hubbard et.al. (7).

The average CO concentration to which each rat was exposed was calculated by integrating the area under a concentration vs time curve from time=0 to time=t_i and dividing the $c*t_i$-product by t_i [average concentration = $(\int C\ dt)/t_i$]. The average temperature,

for those experiments involving elevated temperatures, was similarly determined, i.e., average temperature = $(\int T\,dt)/t_i$.

A scatter plot was constructed for the ambient-temperature CO exposures by plotting t_i as a function of the average CO concentration. A line fitted to these points had the general shape of a rectangular hyperbola with non-zero asymptotes. When an equation of that form was fitted to the data, a negative value was obtained for the t_i asymptote, i.e.,

$$(t_i - [-.604]) * ([CO] - 259) = 32{,}233 \qquad \text{Eq. 1}$$

This would indicate that t_i could be reduced to less than zero by an infinite concentration of CO, which is biologically unlikely, or simply that the form of the equation is inappropriate for describing the concentration-vs-time relationship beyond the experimental limits of this study. A simplified 2-parameter equation of the form,

$$(t_i - 0) * ([CO] - K1) = K2 \qquad \text{Eq. 2}$$

where K1 and K2 are constants, was derived using a standard nonlinear regression technique to obtain

$$t_i = (29995/([CO] - 302)) \qquad \text{Eq. 3}$$

A scatter plot of the data with the fitted-equation line is depicted in Figure 3. Table 1 lists the t_i vs CO concentration data.

In a similar fashion, a scatter plot was constructed from data relating t_i to elevated-temperature exposures (at zero CO concentration) by plotting t_i as a function of the exposure temperature. A simplified 2-parameter equation was derived by the technique used in deriving equation 3 to obtain

$$t_i = 252/([T^{\circ}C] - 35.1) \qquad \text{Eq. 4}$$

A plot of these data, with the fitted-equation line, is depicted in Figure 4. Table 2 lists the corresponding raw data used to derive Eq. 4.

Initial inspection of the combined exposure data indicated that over 90% of the observed t_i's were less than either of the predicted t_i's (from Equations 3 and 4) for the respective temperatures and CO concentrations, indicating that the combined effect was toward a shorter t_i than would be obtained from either exposure condition by itself; exceptions were near the "no-effect" level for one of the parameters. We reasoned that the product (time x temperature) at t_i represented a "dose" analogous to the (time x concentration) value for carbon monoxide. At

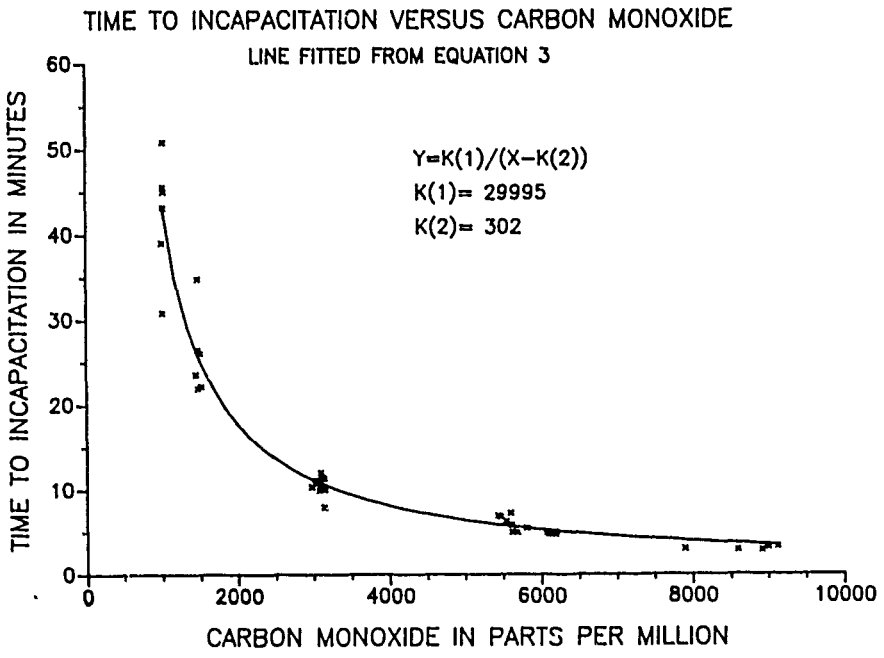

Figure 3. Scatter plot of time-to-incapacitation vs carbon monoxide concentration.

TABLE 1
TIME TO INCAPACITATION FOR CARBON MONOXIDE
AT AMBIENT TEMPERATURE (20°C)

No.	CO PPM	OBSERVED t_1 (min)	No.	CO PPM	OBSERVED t_1 (min)
1	995	39.0	23	3135	10.3
2	1005	30.8	24	3135	10.0
3	1013	50.8	25	5429	6.9
4	1016	43.1	26	5465	6.8
5	1016	45.5	27	5542	6.2
6	1021	45.0	28	5600	7.2
7	1449	23.5	29	5616	4.9
8	1467	21.9	30	5616	5.8
9	1473	34.8	31	5677	4.9
10	1475	26.4	32	5804	5.4
11	1504	26.0	33	6066	4.9
12	1510	22.1	34	6091	4.7
13	2974	10.3	35	6091	4.7
14	3026	11.1	36	6130	4.7
15	3052	11.0	37	6185	4.7
16	3053	10.8	38	6189	5.0
17	3072	9.9	39	7890	2.9
18	3083	10.5	40	8583	2.8
19	3088	12.0	41	8907	2.8
20	3103	11.4	42	8992	3.1
21	3130	11.3	43	9111	3.2
22	3134	7.9			

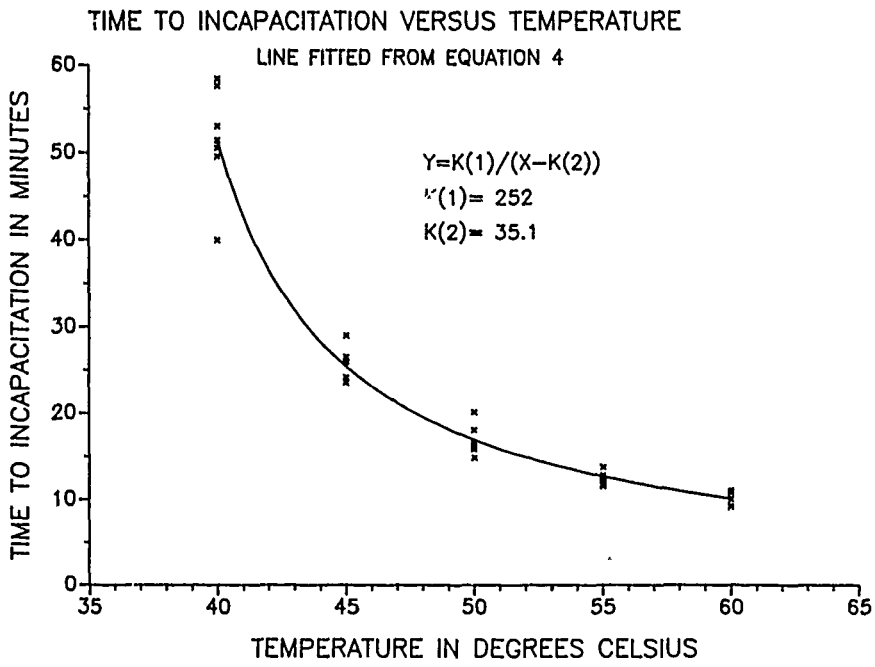

Figure 4. Scatter plot of time-to-incapacitation vs temperature.

TABLE 2
TIME TO INCAPACITATION FOR WHOLE BODY
EXPOSURE AT ELEVATED TEMPERATURES

No.	TEMP °C	OBSERVED t_i (min)	No.	TEMP °C	OBSERVED t_i (min)
1	40	50.5	17	50	15.8
2	40	53.0	18	50	16.0
3	40	39.9	19	50	18.0
4	40	51.4	20	50	20.1
5	40	57.6	21	55	13.7
6	40	58.4	22	55	11.5
7	40	49.5	23	55	11.7
8	45	25.9	24	55	12.2
9	45	26.5	25	55	12.8
10	45	24.1	26	55	12.4
11	45	23.5	27	60	10.0
12	45	26.0	28	60	10.8
13	45	29.0	29	60	10.0
14	50	16.2	30	60	9.2
15	50	14.8	31	60	9.1
16	50	16.6	32	60	11.0

t_i(CO) or t_i(temperature), an incapacitating "dose" had been reached; for any specific time less than these, a fractional dose

was assumed to have been absorbed, and the magnitude of this dose was proportional to time and to the CO concentration (or temperature). Since t_i was inversely proportional to both CO concentration and elevated temperature, the simultaneous application of both was expected to drive the observed t_i in the same direction, i.e., toward a shorter time than was observed for either single condition. This trend was supported by inspection of the combined exposure data.

Although the mechanisms for incapacitation from heat exhaustion and from carbon monoxide inhalation are surely different, we felt that an empirical equation derived from the observed times-to-incapacitation of rats responding to the combined effects of defined temperature and CO concentration would be useful in estimating the effect of the thermal contribution when the test temperature exceeds the calculated t_o of 35.1°C (if only for the narrow range of temperatures in this study). For an exactly additive effect, we reasoned that the sum of the reciprocal t_i's for CO and temperature would equal the reciprocal of the observed t_i, that is,

$$1/t_{i(\text{for CO})} + 1/t_{i(\text{for temp})} = 1/t_{i(\text{observed})} \qquad \text{Eq. 5}$$

Since an "exactly additive" effect was unlikely for two dissimilar mechanisms, we judged that a more likely form for the equation might be,

$$K_1/t_{i(\text{for CO})} + K_2/t_{i(\text{for temp})} = 1/t_{i(\text{observed})} \qquad \text{Eq. 6}$$

where K_1 and K_2 are weighting factors for the two effects. By performing a multiple linear regression relating the calculated t_i's for CO and temperature to the observed t_i's for the combined effects, and using the algorithm that forces the intercept to equal zero, the least-squares estimates for K_1 and K_2 were 0.78 and 0.66, respectively. The working equation for predicting the combined effects of CO toxicity and elevated air temperature became,

$$1/t_i = [0.78*([CO-302]/29995)] + [0.66*([T^{\circ}C-35.1]/252)] \qquad \text{Eq. 7}$$

The relationship presented as equation 7 can be used to predict response time to CO concentrations and whole-body thermal environments within the limits used in the original exposures. Table 3 lists the numerical values for observed t_i's and predicted t_i's (from Eq. 7) for the 63 combined exposures.

TABLE 3
COMBINED EFFECTS OF CARBON MONOXIDE AND ELEVATED TEMPERATURE ON TIME TO INCAPACITATION

No.	CO,ppm	Temp,°C	CALC t_i from CO	CALC t_i from temp	OBSERVED t_i,min	CALC t_i CO + TEMP
1	986	40.0	44.2	51.8	33.2	33.2
2	1001	40.0	43.2	51.8	37.0	32.8
3	1002	40.0	43.2	51.8	36.1	32.7
4	1010	40.0	42.7	51.8	41.7	32.5
5	1013	40.0	42.5	51.8	32.8	32.4
6	1017	40.0	42.2	51.8	31.0	32.3
7	1505	40.0	24.7	51.8	19.2	22.9
8	1509	40.0	24.6	51.8	18.8	22.8
9	1531	40.0	24.2	51.8	20.5	22.5
10	1567	40.0	23.5	51.8	17.0	22.1
11	1568	40.0	23.5	51.8	17.7	22.1
12	1592	40.0	23.0	51.8	29.8	21.8
13	3118	40.0	10.5	51.8	8.9	11.7
14	3141	40.0	10.4	51.8	9.2	11.6
15	3212	40.0	10.1	51.8	8.2	11.4
16	1003	45.0	43.1	24.2	20.3	22.0
17	1005	45.0	43.0	24.2	25.5	22.0
18	1009	45.0	42.7	24.2	25.2	22.0
19	1014	45.0	42.4	24.2	24.2	21.9
20	1015	45.0	42.4	24.2	21.1	21.9
21	1026	45.0	41.7	24.2	25.5	21.8
22	1484	45.0	25.2	24.2	18.2	17.3
23	1488	45.0	25.1	24.2	14.9	17.2
24	1493	45.0	25.0	24.2	16.3	17.2
25	1497	45.0	24.9	24.2	13.1	17.2
26	1500	45.0	24.8	24.2	21.9	17.1
27	1512	45.0	24.6	24.2	17.6	17.0
28	1866	44.6	18.9	25.2	14.9	15.0
29	1878	45.0	18.8	24.2	14.9	14.7
30	1906	45.0	18.5	24.2	15.0	14.5
31	3262	45.0	10.0	24.2	9.0	9.6
32	3275	45.0	9.9	24.2	9.3	9.6
33	3288	45.0	9.9	24.2	9.9	9.6
34	961	50.0	46.0	16.3	16.3	17.3
35	1004	50.0	43.0	16.3	15.9	17.0
36	1098	50.0	37.8	16.3	16.1	16.3
37	1537	50.0	24.1	16.3	14.6	13.7
38	1538	50.0	24.1	16.3	15.1	13.7
39	1563	50.0	23.6	16.3	14.9	13.6
40	3170	50.0	10.3	16.3	10.1	8.7
41	3192	50.0	10.2	16.3	9.4	8.6
42	3218	50.0	10.1	16.3	9.8	8.6
43	996	55.0	43.6	12.5	12.7	14.1
44	1006	55.0	42.9	12.5	13.5	14.1
45	1033	55.0	41.3	12.5	12.6	13.9
46	1589	55.0	23.1	12.5	11.7	11.6
47	1592	55.0	23.0	12.5	11.4	11.6
48	1599	55.0	22.9	12.5	12.3	11.5
49	3119	55.0	10.5	12.5	8.2	7.9
50	3193	55.0	10.2	12.5	8.8	7.8
51	3274	55.0	9.9	12.5	8.8	7.7
52	1033	60.0	41.3	10.4	9.0	12.1
53	1044	60.0	40.6	10.4	9.6	12.0
54	1044	60.0	40.6	10.4	9.9	12.0
55	1602	59.8	22.9	10.4	10.4	10.3
56	1612	60.0	22.7	10.4	10.1	10.2
57	1613	59.8	22.7	10.4	10.0	10.2
58	3008	58.9	10.9	10.8	8.2	7.6
59	3037	59.1	10.8	10.7	8.2	7.5
60	3047	58.5	10.7	10.9	7.3	7.6
61	3072	59.2	10.7	10.7	8.1	7.5
62	3121	59.5	10.5	10.6	8.0	7.3
63	3130	59.5	10.4	10.6	7.9	7.3

Figure 5 is a plot of the correspondence between the two sets of values; a least squares regression line to fit the data is described by the equation,

$$t_{i(predicted)} = [2.6 + (0.84) * t_{i(observed)}].$$

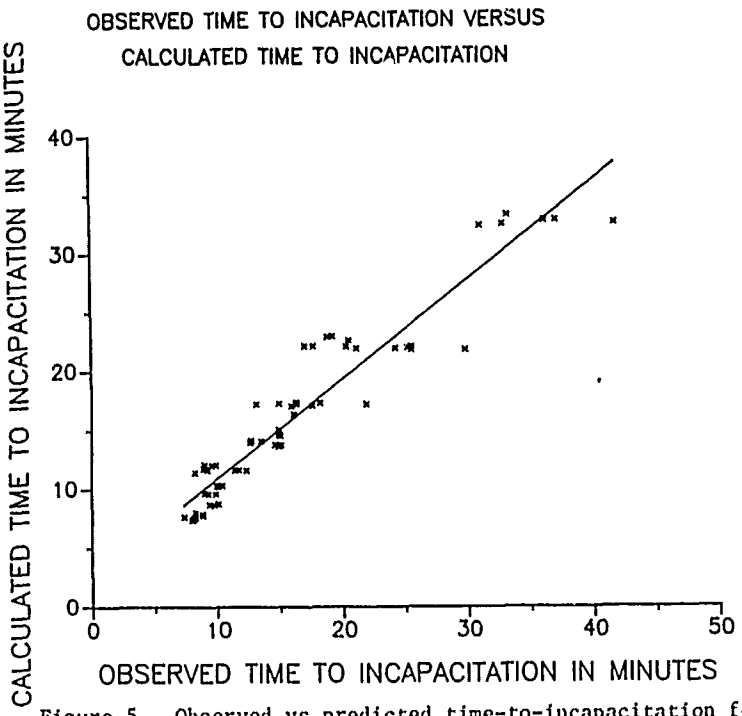

Figure 5. Observed vs predicted time-to-incapacitation for rats exposed to CO at elevated temperatures.

To graphically display the variation of t_i to changes in the thermal environment at the nominal CO concentrations of 0, 1000, 1500, and 3000 ppm, we plotted the mean observed t_i's at each temperature and concentration, as shown in Figure 6. A similar treatment of the data was employed for Figure 7 to show the variation in t_i with CO concentration for each temperature. In both graphs, lines between points are drawn to differentiate treatments, and do not indicate continuous values between points; vertical bars indicate the standard error of the mean ($s/\sqrt{n}$) for all observed t_i's at each point.

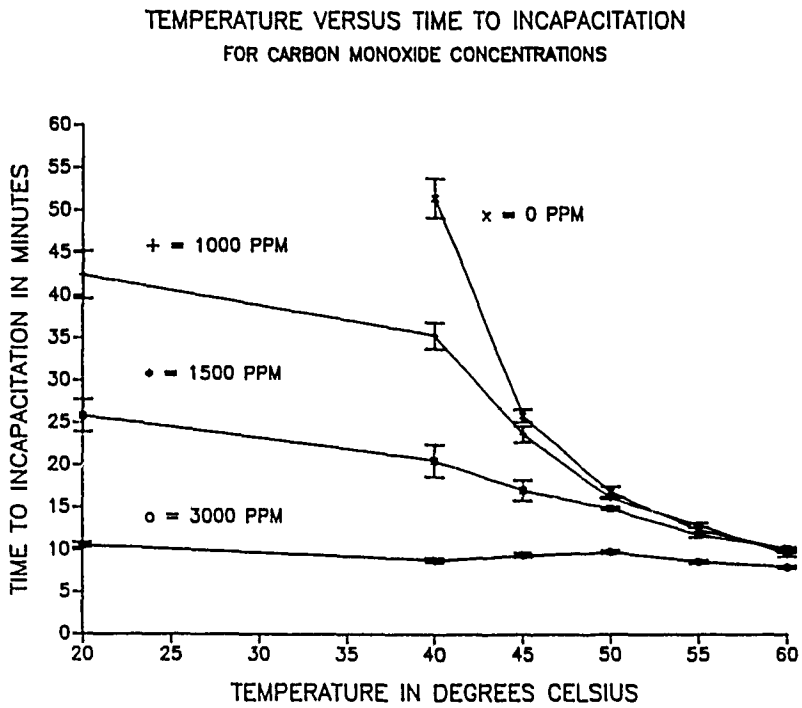

Figure 6. Variation in time-to-incapacitation with temperature at 3 carbon monoxide concentrations.

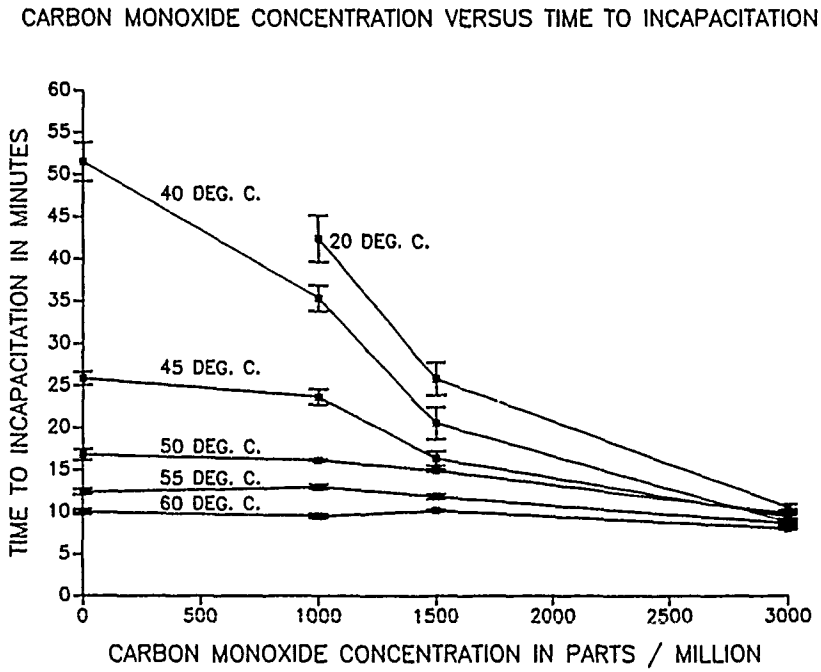

Figure 7. Variation in time-to-incapacitation with carbon monoxide concentration at 5 temperatures.

SUMMARY AND CONCLUSIONS

Laboratory rats were exposed to CO in air, to whole-body thermal environments from 40-60°C, and to selected CO concentrations in elevated temperature environments. For each animal, and for each exposure condition, the time to physical incapacitation (t_i) was measured using a motor-driven rotating cage assembly.

The response times for experiments using CO exposures alone, and for those using elevated temperatures alone, were plotted against the respective concentrations or temperatures, and equations were derived by nonlinear regression techniques to mathematically describe these relationships. The resulting equations, for time-to-incapacitation, are:

$$t_i = 29995/([CO] - 302) \quad \text{(for carbon monoxide)}$$

and

$$t_i = 252/([T°C] - 35.1) \quad \text{(for elevated temperatures of 40-60°C)}$$

where t_i is in minutes, [CO] is the carbon monoxide concentration in parts-per-million by volume, and [T°C] is the whole-body exposure temperature in degrees Celsius. The observed response times obtained at selected concentrations of CO at elevated temperatures were analyzed with respect to the predicted response times for individual CO and temperature effects.

We concluded from this analysis that incapacitation occurs earlier when CO inhalation is combined with elevated whole-body temperatures than is observed in exposures to the same CO concentrations and thermal parameters individually. Response deviations are more prominent for elevated temperatures combined with low CO concentrations, and for low temperature exposures combined with higher CO concentrations, that is, when one parameter becomes the controlling factor in mediating the animal response. The mechanistic hypothesis that is supported by the data is that the incapacitating effects of CO and of elevated temperatures are fractionally additive when simultaneously applied. This reaffirms the need for adequate temperature control in experiments where the rat model is used to integrate the toxic effects of combustion gases. With the caveat that estimates be limited to the CO and temperature ranges of the original data, we offer an equation that may be useful in estimating the time-to-incapacitation produced by the inhalation of CO in an elevated temperature environment:

$$t_i = \left(\frac{1}{[0.78*([CO]-302)/29995] + [0.66*([T°C]-35.1)/252]} \right) .$$

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